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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/11/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/741,669	Applicant(s) FORSYTH ET AL.	
	Examiner Frank W Lu	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-131* is/are pending in the application.

4a) Of the above claim(s) *1-44 and 57-131* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,12,18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on December 17, 2002 has been entered as Paper No:20. Since amended claim 128 is directed to a method for manufacturing an antibiotic compound and claim 45, which claim 128 is dependent on, is directed to a method for identifying a compound, claim 128 is not considered to be independent or distinct from the invention originally claimed wherein original filed claim 128 comprises a screening step using the method of claim 45. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 128 has been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. The claims pending in this application are claims 1-131 with claims 1-44 and 57-131 withdrawn from consideration as the result of the restriction requirement. Rejection and or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment. Claims 45-56 will be examined.

Election/Restriction

2. This application contains claims 1-44 and 57-131 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

3. Claim 55 is objected to because of the following informality: the phrase "selected from the group" should be deleted since this claim only has one SEQ ID No.

4. Claim 56 is objected to because of the following informality: "an RNA" should be "a RNA".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 45-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Applicant is referred to the interim guidelines on written description published on December 21, 1999 in the Federal Register at Volume 64, Number 244, pp.71427-71440.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117.

The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification (pages 41 and 42, and Sequencing listing) provides adequate written descriptions for SEQ ID: 60, which is a nucleotide sequence of Yid C from E.Coli wherein Yid C is a evolutionarily conserved protein that can mediate membrane protein assembly in bacteria (see a review from Chen *et al.*, Biol. Chem., 383, 1565-1572, October 2002). However, the specification fails to adequately describe that a nucleic acid comprising a nucleotide sequence of SEQ ID: 60 can be used as an antisense nucleic acid and an antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. Furthermore, from the specification, it is unclear that SEQ ID No: 60 is a genomic sequence of Yid C or full or partial cDNA sequence of Yid C. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998).

In this instant case, although the specification adequately describes SEQ ID NO: 60, the specification fails to adequately describe that a nucleic acid comprising a nucleotide sequence of

SEQ ID: 60 can be used as an antisense nucleic acid and an antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. Therefore, the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

With limited disclosure provided by the specification, the skilled artisan cannot envision whether a nucleotide sequence of SEQ ID: 60 can be used as an antisense nucleic acid and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co.* Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what e has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. Claims 45-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance to produce a sensitized cell by reducing the activity or amount of a gene product in any kind of cell by expressing a sub-lethal level of any kind of antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether a sensitized cell can be produced by reducing the activity or amount of a gene product in any kind of cell by expressing a sub-lethal level of any kind of antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60.

Claims 45-56 are directly to a method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism by reducing the activity or amount of a gene product in any kind of cell by expressing a sub-lethal level of any kind of antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. The specification only describes that SEQ ID No: 60, which is a nucleotide sequence of Yid C from E.Coli wherein Yid C is a evolutionarily conserved protein that can mediate membrane protein assembly in bacteria (see a review from Chen *et al.*, Biol. Chem., 383, 1565-1572, October 2002). However, the specification does not provide a guidance to produce a sensitized cell by reducing the activity or amount of a gene product in any kind of cell by expressing a sub-lethal level of any kind of antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. Since the specification does not show that a nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60 can serve as an antisence nucleic acid, it is unclear whether a cell contains a nucleic acid encoding a gene product whose expression is inhibited by a nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60 by antisense mechanism. If there is no such nucleic acid in the cell, an antisense nucleic acid of such nucleic acid can not found in the cell either. Therefore, it is impossible to reduce the activity or amount of a gene product in the cell by expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an

antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60 and produce a sensitized cell.

Applicant may argue that, in view of SEQ ID No: 60, a skilled artisan can use a nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60 as an antisense nucleic acid to inhibit some gene in a cell. However, without providing a convinced evidence, this argument is not persuasive because it is known that the art of antisense therapy is highly unpredictable (see Bennett, Biochem Pharmacol. 55:9-19, 1998, page 9, col.1, line 19-23). The art clearly emphasize that expectations of current antisense therapy has been over sold and has factually provided only a limited success (see Branch, TIBS, 23 Feb, 45-50, 1998, page 46 col.2. para.3; Gura, Science 270:575-577, 1995). Because it is difficult to predict the what portion of an RNA molecule would be accessible in-vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside the cells. The efficacy of antisense therapy is further compounded by the fact that base compositions as well as the secondary and tertiary structure of the target nucleotide sequence determines the accessibility of the sequence to an antisense sequence (see Branch, page 47 col.2 para.3, page 49, col.1, para 3). Furthermore, in inside cells, it is not possible to improve antisense specificity by rising temperature or ionic strength, therefore alternative strategies are required to enhance specificity within cells (see Branch, page 48, col.3, para.3). It is not yet clear whether in-vitro screening techniques would identify antisense nucleotide that are effective in-vivo because cellular proteins and ribonucleoproteins complexes in plasma prevent the binding of.an antisense to target nucleotide sequence (see Branch, page 49, col.1 para.2, col. 3 para. 2). In addition the deliver of

anisense to target site is problematic because oligonucleotides are not distributed uniformly with in a tissue but accumulate within certain cell population such as kidney (see Bennett, page 10 col.2, para 2-3). The antisense therapy is not a routine scientific endower for the reasons mentioned above. Significant trial and error experimentation is required to practice the antisense technology particularly when the antisense are used for a therapeutic purpose in-vivo (see Crooke, Antisense & Nucleic Acid Drug Dev. 8:115-122, 1998, page 115, col.1 para.3). The art clearly teaches that the delivery and expression of a therapeutic gene via gene therapy was not only problematic in past but is also the case in present despite the various advances in the field of gene therapy. Furthermore, even through we assume that SEQ ID NO: 60 can be used as an antisense nucleic acid in E. Coil, it is unclear whether SEQ ID NO: 60 can be used as an antisense nucleic acid in any kind of cell as recited in claims 45-56 because the specification does not provide an evidence to show that SEQ ID NO: 60 is conserved in all species and can be used as an antisense nucleic acid in any kind of cell.

With these unpredictable factors, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. These undue experimentation at least includes to test whether a nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60 can serve as an antisence nucleic acid in a cell and whether a cell contains a nucleic acid encoding a gene product whose expression is inhibited by a nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60 by antisense mechanism.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 45-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 45 are rejected as vague and indefinite in view of the phrase "reducing the activity or amount of a gene product in a cell by expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60" because it is unclear that "a gene product in a cell" and "a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60" are the same molecule or not since, from the claim, it seems that two gene products can be the same or can be different. Please clarify.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. No claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
March 10, 2003

Ethan Whisenant, Ph.D.
Primary Examiner (FSA)